PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>R 41445 | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/EP 03/07389 | International filing date *(day/month/year)*<br>09.07.2003 | Priority date *(day/month/year)*<br>12.07.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>C07K14/47 | | |
| Applicant<br>AXON NEUROSCIENCE FORSCHUNGS-UND ENTWICKLUNGS GMBH | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 26.01.2004 | 02.11.2004 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Giebeler, K<br>Telephone No. +49 89 2399-8546 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07389

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-70 as originally filed

**Claims, Numbers**

1-23 as originally filed

**Drawings, Sheets**

1/20-20/20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 3,4,7,8,21 (all completely);9-13,19,20,22 (all partially)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 21 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 3,4,7,8 (all completely); 9-13,19,20-22 (all partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1,2,14,15,23 (all completely);9-13,19,20,22 (all partially) .

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 12,13,15,19,20 |
| | No: | Claims | 1,2,9-11,14,22,23 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1,2,9-15,19,20,22,23 |
| Industrial applicability (IA) | Yes: | Claims | 1,2,9-15,19,20,22,23 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 22 is so inadequately supported by the description that no meaningful opinion could be formed; no vaccine has actually been disclosed in the application.

**Re Item IV**

**Lack of unity of invention**

The International Preliminary Examining Authority shares the opinion of the International Searching Authority that the application lacks unity of invention, since the claims are directed to four separate inventions as follows:

(1) Claims 1, 2, 14, 15, 22, 23 (all completely); claims 9-13, 19-21 (all partially)

(2) Claims 3, 4 (all completely); claims 9-13, 19-21 (all partially)

(3) Claims 5, 6, 16-18 (all completely); claims 9-13, 19-21 (all partially)

(4) Claims 7, 8 (all completely); claims 9-13, 19-21 (all partially)

The general inventive concept underlying the 4 groups of invention of the present application can be seen as N- and C-terminally double truncated tau molecules detectable in Alzheimer's diseased brain tissue and not detectable in normal healthy brain tissue. However, this general inventive concept is not novel having regard to the prior art as illustrated e.g. by document WO96/30766 or EMBO J. (1993) 12: 365-370, each of which discloses a tau fragment with the amino acid sequence of SEQ ID NO:1 (see Figure 22 of WO96/30766; Figure 1, peptide d/GAE of EMBO J.), which is encompassed by claims 1 and 2 (group (1)).

In the light of the prior art, the problem underlying the application can be defined as the provision of further N- and C-terminally double truncated tau molecules. This problem is solved by providing N- and C-terminally double truncated tau molecules as defined in independent claims 1, 3, 5 and 7 showing different kinds of activities:

Invention (1) solves the problem by providing tau molecules which prevent normal tau protein from promoting microtubule assembly in an in vitro microtubule assembly assay.
Invention (2) solves the problem by providing tau molecules which do not prevent wild type tau from promoting microtubule assembly in an in vitro microtubule assembly assay.
Invention (3) solves the problem by providing tau molecules which have a higher microtubule assembly promoting activity than wild type tau in an in vitro microtubule assembly assay.
Invention (4) solves the problem by providing tau molecules which have a pathological microtubule assembly promoting activity different from wild type tau in an in vitro microtubule assembly assay.

Due to the prior art disclosing a polypeptide according to group (1), and due to the fact that no other technical features common to the different solutions can be distinguished, which in the light of the prior art could be regarded as special, this authority is of the opinion that there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The documents of the state of the art are numbered D1 to D8 according to their respective position in the International Search Report.

2. The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the documents D5 to D7 cited in the international search report could become relevant.

3. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 2, 9-11, 14, 22 and 23 is not new in the sense of Article 33(2) PCT.

   N- and C-terminally double truncated tau molecules detectable in Alzheimer's

disease brain tissue have already been described in the prior art. In particular, a polypeptide with the amino acid sequence of SEQ ID NO:1 as disclosed in the application was already known from D1 (see Figure 22, SEQ ID NO:6 and page 38, lines 1-4) which is considered to be prejudicial to the novelty of at least claims 1, 2, 14, 22 and 23. The polypeptide of SEQ ID NO:1 and the antibody mAB 423 have been disclosed in D2 (see Figure 1, peptide "d/GAE") which is prejudicial to the novelty of at least claims 1, 2, 22 and 23. The recombinant expression of said protein in E. coli and its use in the microtubule assembly assay have been disclosed in D3 which destroys the novelty of at least claims 1, 2, 9-11, 14, 22 and 23.

4. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 12, 13, 15, 19 and 20 does not involve an inventive step in the sense of Article 33(3) PCT.

   Concerning claims 12 and 13, it is pointed out that the purification of Alzheimer's tau proteins by gel filtration was generally known, see for instance D1, page 12, lines 32-34. Moreover, the use of a cellular system in methods of testing (claim 15) and the generation of transgenic animals and their use (claims 19 and 20) were standard techniques at the present priority date (see also D8).

5. It is also pointed out that claim 1 is considered to lack clarity (Article 6 PCT) since the claimed molecules are insufficiently defined; it is not clear which parts of the tau protein should be present in order to perform the specified function.

   It is not entirely clear which antibodies are encompassed by the definition of claim 23, which is apparently not limited to the deposited antibody DC44.